AMENDMENTS TO THE DRAWINGS

The attached replacement sheets of drawings includes changes to Fig. 10 and Fig. 11, and replaces the original sheets including Fig. 10 and Fig. 11.

In Fig. 10, the structures have been renumbered as Fig. 10A, Fig. 10B, and Fig. 10C. In Fig. 11, the top and bottom panels have been renumbered as Fig. 11A and Fig. 11B, respectively, as shown in the annotated sheets on the following pages.

ANNOTATED SHEET

KAD

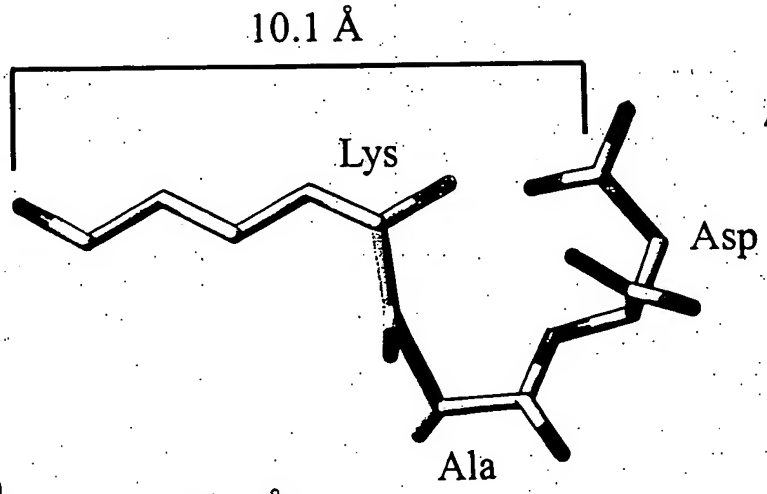


FIG. 10A

KAD

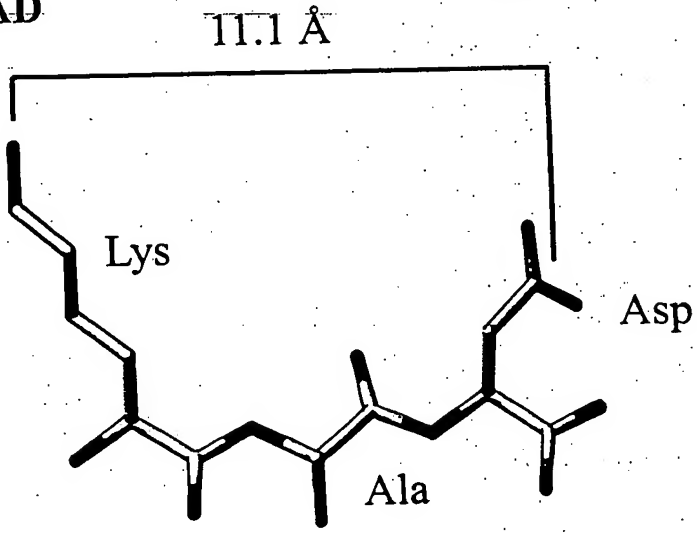


FIG. 10B

KFFE

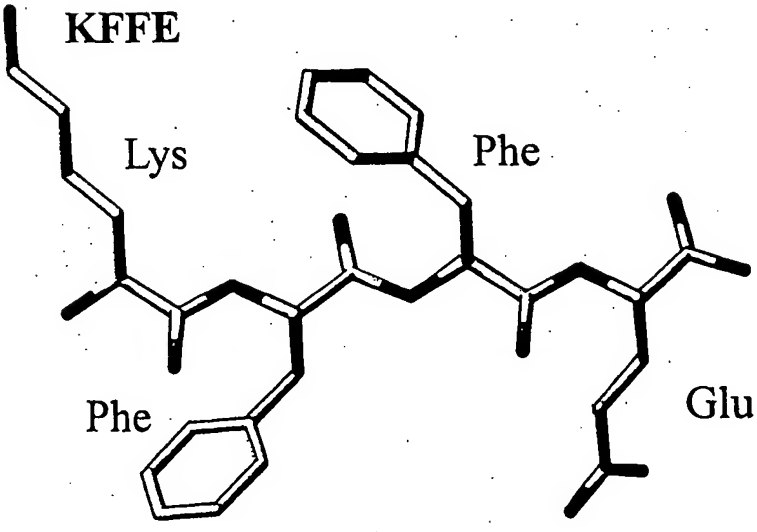


FIG. 10C

FIG. 10

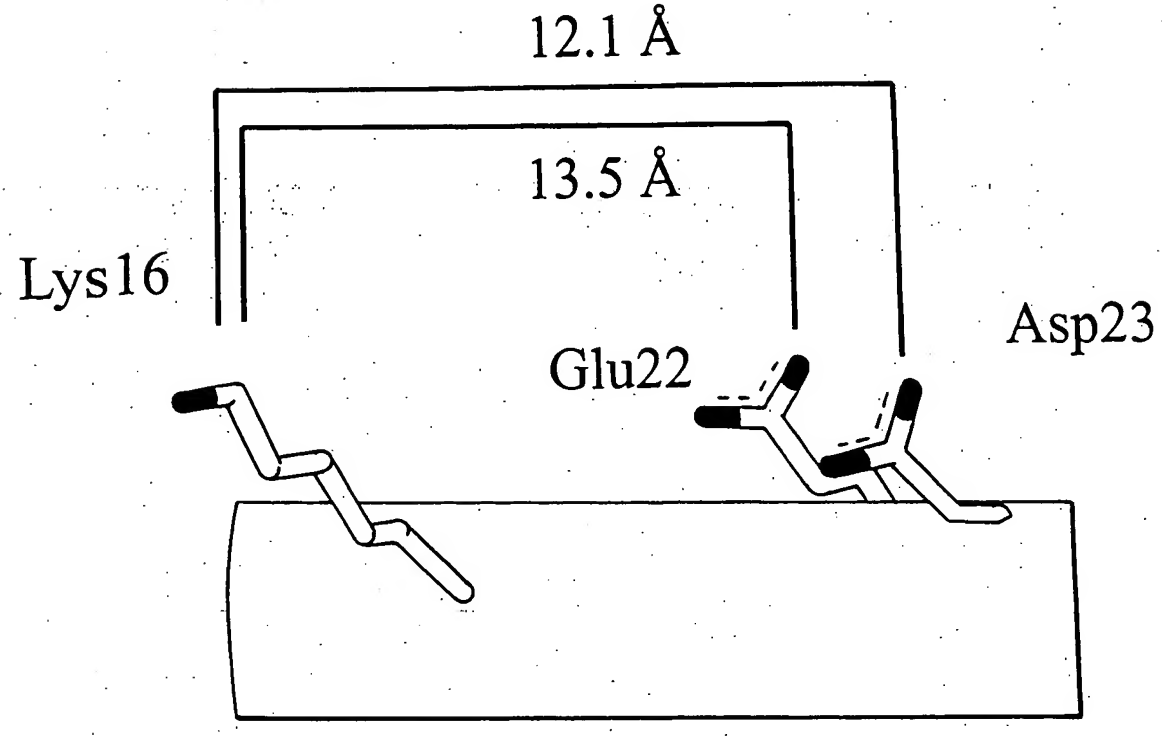


FIG. 11A

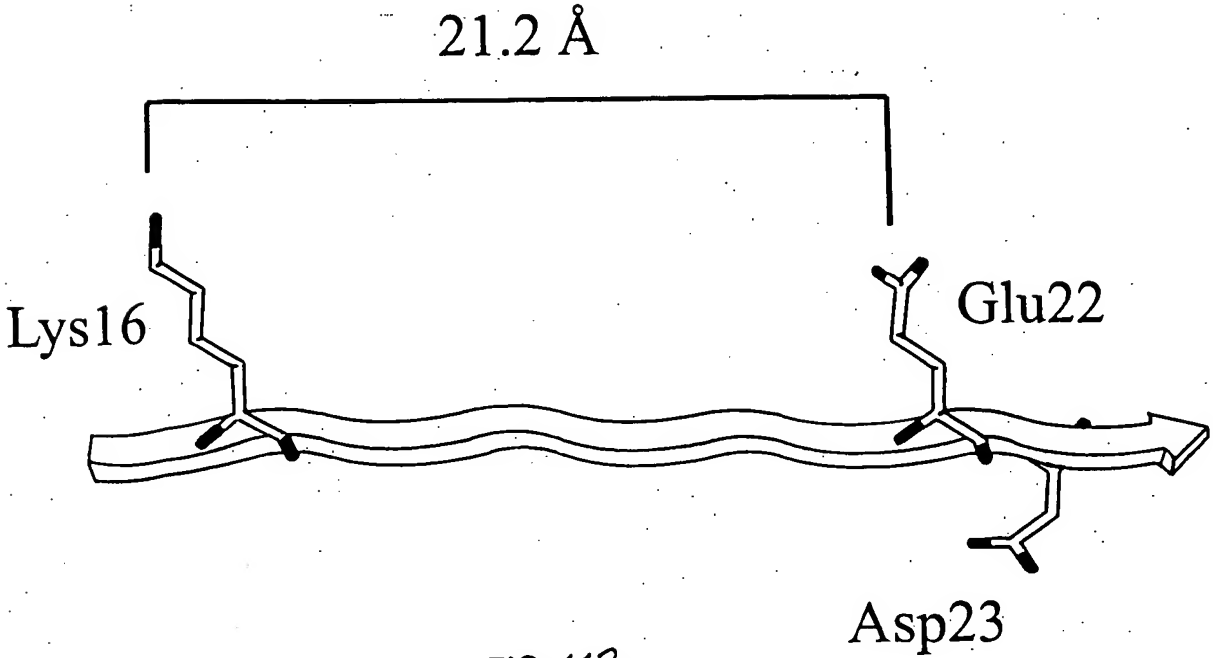


FIG. 11B

REMARKS

Claims 5-9 are pending in the present application. The specification has been amended to update the cross references to related applications, to incorporate the alteration on page 6 of the application as filed, and to reflect amendments to the labeling of Figures 10 and 11. Applicants believe that no new matter is added by the amendments.

Drawings

The drawings have been amended to separately label the components of Figures 10 and 11. The specification has been amended to reflect these changes.

35 U.S.C. § 102 (b)

Claims 5-9 have been rejected under 35 U.S.C. 102 (b) as allegedly anticipated by Soto et al. (*Biochem. Biophys. Res. Com.* 1996; 226:672-680). Applicants respectfully disagree with the rejection.

Applicants' claimed invention relates to a method of identifying whether a protein is susceptible to forming amyloid by analyzing the protein for predicted discordant helix, a method of decreasing the rate of formation of beta-strand structure between discordant helix-containing polypeptides with a compound that stabilizes the alpha-helical form of the polypeptide, and a method of treating an individual having or at risk for an amyloidosis using a therapeutically effective amount of a compound that stabilizes an alpha-helical form of a discordant helix polypeptide that can form amyloid. Key to the claimed invention is the recognition of discordant helix and stabilization of an α-helical form of a disclordant helix.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. (*Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)).

Soto et al. provides no teaching about discordant helix, indeed there is no indication that Soto et al are aware of such a structure. Because Soto et al. does not even recognize such a structure, it cannot teach stabilizing an α-helical form of a discordant helix. Indeed, Soto does not suggest stabilizing an α-helical form, but rather is directed to binding peptides to a β-sheet form of an Aβ peptide. Because Soto et al. does not teach discordant helix and does not teach

stabilization of the alpha helical conformation of a discordant helix, Soto et al. cannot anticipate the claimed invention.

Claim 5

Claim 5 is drawn to

> A method of identifying whether a protein is susceptible to forming amyloid, the method comprising analyzing the amino acid sequence of the protein to determine whether the protein contains a predicted discordant helix, wherein the presence of predicted discordant helix is an indication that the protein is susceptible to forming amyloid.

The present specification defines discordant helix:

> A "discordant helix" is an amino acid sequence that is predicted to be able to form an α-helix and is also predicted to be able to form a β-strand. A discordant helix can be identified using structure analysis programs that predict secondary structure of polypeptides, specifically by analyzing an amino acid sequence for predicted α-helix and also analyzing the amino acid sequence for predicted β-strand. A sequence that is predicted to form α-helix and β-strand is a discordant helix.

Soto et al. does not disclose any method for identifying a protein susceptible to forming amyloid, much less a method for identifying such proteins by identifying discordant helix. In fact, there is nothing in Soto et al. disclosing discordant helix.

Soto et al. does disclose the presence of hydrophobic residues in an Aβ peptide and the theory that "Aβ assembly is partially driven by hydrophobic interactions." (Soto et al. at page 672). But Soto et al. does not even suggest identification of hydrophobicity as a method of identifying a protein susceptible to forming amyloid,. Indeed, proteins are known in the art that have hydrophobic regions, but which are not proteins that form amyloid.

The Office Action appears to allege that Soto et al. teaches a number of features of the claimed invention;

> Soto et al., teach that pH, peptide concentration, and solvents can influence the conformation of Aβ peptides) p.675 [sic], first

> paragraph). These factors can determine whether the Aβ peptide adopts an α-helix or a β-sheet conformation. Soto et al., teach that hydrophobicity facilitates monomeric interactions that thermodynamically drive Aβ peptides to convert from α-helices to β-sheets, which produce amyloid fibrils (p. 673, first paragraph).

Regardless of whether the characterization of Soto et al. is correct, nothing in this characterization corresponds to a teaching of peptide sequences that form discordant helix.

The Office Action also states

> Soto et al., teach that hydrophobicity facilitates monomeric interactions that thermodynamically drive Aβ peptides to convert from α-helices to β-sheets, which produce amyloid fibrils (p. 673, first paragraph).

This is not what Soto et al. teaches. In what appears to be the relevant section, Soto et al. states "[i]t seems likely that hydrophobicity facilitates monomeric interaction and that β-sheet content drives this interaction to β-sheet oligomers and amyloid fibrils. (Soto et al. at p. 673, first paragraph). In this passage, Soto et al. appears to be discussing the monomeric interaction between β-conformation monomers to make β-sheet, and makes no reference to α-helical forms. Applicants submit that the Office Action has misunderstood the meaning of the recited section of Soto et al.

The Office Action also states "Soto et al., teach the limitations of a 'discordant helix' as defined in the instant disclosure (p. 4) as an amino acid sequence that is predicted to be able to form either an α-helix or β-sheet. (p. 674, Figure 1). (Office Action at page 3, third paragraph). Applicants maintain that this is incorrect. As discussed above, the definition of a discordant helix includes "[a] 'discordant helix' is an amino acid sequence that is predicted to be able to form an α-helix and is also predicted to be able to form a β-strand." Figure 1 of Soto et al. shows an "amino acid sequence and β-sheet probability" for selected sequences. It does not provide information as to α-helix for those sequences, which is required for identification of a discordant helix. Thus, Soto et al. does not teach the limitations of a discordant helix

Because Soto et al. does not disclose the features of claim 5, e.g., it does not disclose discordant helix, it does not disclose a method of identifying a protein that can form amyloid, it

does not disclose a method of identifying a protein that can form amyloid by predicting whether a protein can form discordant helix, the reference cannot anticipate claim 5.

Claim 6 depends from claim 5, and stipulates that the identified discordant helix is at least six amino acids in length. The Office Action (at page 3, third paragraph) states

> Soto et al., also teach the use of an inhibitor of Aβ fibrillogenesis peptide 1 (iAβ1), an 11 amino acid peptide, to prevent the adoption of β-sheets in Aβ so that the maintenance of α-helices is favored (p. 674, second parargraph).

The Soto et al. language that appears to be referenced by the Office Action literally states

> ...we first designed an 11 amino acid peptide, called inhibitor of Aβ fibrillogenesis peptide 1 (iAβ1) (Fig 1A). The circular dichroism spectrum of iAβ1 in aqueous solution was typical of unordered structures under all the conditions tested and the peptide did not aggregate even at high concentrations... (Soto et al. at page 674, second paragraph)

This paragraph reports features of a peptide generated by the authors of Soto et al. The paragraph appears to indicate that the synthetic peptide, iAβ1, does not aggregate with itself. If this passage has been cited by the Office Action as part of the rejection of claim 6, Applicants point out that this passage appears to have nothing to do with the identification of a discordant helix that is at least six amino acids in length. Applicants also note that nothing in this passage, suggests that the iAβ1 peptide stabilizes α-helix, and therefore, this passage appears to be irrelevant to the claimed invention.

The Office Action points out the lengths of the iAβ1 peptide and derivatives that were synthesized by Soto et al. Applicants assume that this is with reference to claim 6. As discussed above, there is no disclosure in Soto et al. of discordant helix or methods of identifying a protein that is susceptible to forming amyloid. Because Soto et al. does not teach any method of identifying protein susceptible to forming amyloid, does not even recognize the existence of discordant helix, and does not disclose stabilization of α-helix is a discordant helix, Soto et al. does not anticipate claim 6.

Claim 7 is drawn to

> A method of decreasing the rate of formation of β-strand structures between at least two discordant helix-containing polypeptides, the method comprising contacting the discordant helix-containing polypeptides with a compound that stabilizes an α-helical form of the discordant helix.

As discussed above, nothing in Soto et al. relates to the identification of discordant helix, nor does Soto et al. suggest the stabilization of an α-helical form of a discordant helix. The peptide disclosed in Soto et al. is designed

> based on the hypothesis that amyloid formation could be inhibited by peptides homologous to Aβ and with a similar degree of hydrophobicity, but with a very low propensity to adopt a β-sheet conformation." (Soto et al. at p. 673).

There is no suggestion by Soto et al. to stabilize an α-helix conformation of a peptide, nor is there any evidence of an effect by the inhibitor peptide of Soto et al. on α-helix conformation. Because of the deficiciencies of Soto et al., the reference cannot anticipate claim 7 or any other pending claim.

Claim 8 is drawn to a method of treating an individual having or at risk for an amyloidosis by administering a therapeutically effective amount of a compound that stabilizes an α-helical form of a discordant helix-containing polypeptide that forms amyloid. As discussed above, nothing in Soto et al. suggests making such a compound, much less treating a subject with such a compound. Accordingly, Soto et al. does not anticipate Claim 8.

Claim 9 depends from claim 8. For the reasons discussed above, Soto et al., does not anticipate claim 8. Furthermore, Soto et al. provides no teaching related to prion disease and therefore cannot anticipate this feature of claim 9.

The Office Action also states

> Soto et al., also teach a method of determining the percentage of amyloid formed per concentration of iAβ1... thus showing that the smaller peptide inhibitors are able to successfully decrease the rate of formation of β-strand structures. Soto et al., teach that the anti-β-sheet peptides and derivatives, including cyclic peptides or peptide mimetic molecules may be used to prevent and/or retard amyloidosis in vivo in Alzheimer's disease and other types of amyloid related disorders (p. 678, last paragraph to p. 679, first paragraph)

Applicants do not understand the relevance of this passage. In fact, in the paragraph preceding the cited section, Soto et al. states

> "The results of this study support the concept that the formation of a β-sheet secondary structure is related to fibrillogenesis. It is likely that anti-β-sheet peptides inhibit amyloid formation by binding to monomeric Aβ peptides thereby blocking the formation of the oligomeric β-sheet conformation precursor of the fibrils.

Thus, Soto et al. may teach blocking of binding between entities that are in a β-conformation. This is not the same approach as that taught by Applicants', which relates to stabilization of a protein that contains a discordant helix in an α-helical conformation.

In view of the arguments presented above, Applicants believe that Soto et al. does not anticipate any of the pending claims and respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

CONCLUSION

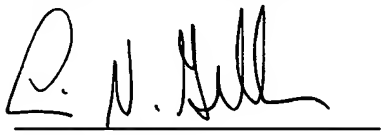
In view of the arguments presented above, Applicants believe the pending application is in condition for allowance, which action is respectfully requested.

A Petition for Extension of Time is enclosed herewith. No additional fees are believed to be due. However, if such a fee is due or a credit is owed, please make them to our Deposit Account No. 08-0219.

The Examiner is encouraged to telephone the undersigned at the number listed below in order to expedite the prosecution of this application.

Respectfully submitted,

Dated: March 29, 2006



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Attachments